### The Utilization of Epilepsy Surgery – Potential Gaps and Future Directions

<table>
<thead>
<tr>
<th>Time (mins)</th>
<th>Speaker (affiliation)</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>Mark Keezer (Université de Montréal)</td>
<td>Patterns of utilization of epilepsy surgery</td>
</tr>
<tr>
<td>20</td>
<td>Walter Hader (University of Calgary)</td>
<td>The Canadian Epilepsy Surgery Survey (CESS)</td>
</tr>
<tr>
<td>20</td>
<td>Nathalie Jetté (Icahn School of Medicine at Mount Sinai)</td>
<td>Barriers and strategies to improve access to epilepsy surgery</td>
</tr>
<tr>
<td>20</td>
<td>Carter Snead III (University of Toronto)</td>
<td>The Ontario Comprehensive Epilepsy Care program</td>
</tr>
<tr>
<td>25</td>
<td>All speakers</td>
<td>Questions &amp; panel discussion</td>
</tr>
</tbody>
</table>
Presenter disclosure

Faculty: Mark Keezer

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None to report.
Mitigating potential bias

The disclosed relationships bear no relationship to the topic of the presentation(s) today.
Patterns of utilization of epilepsy surgery
Looking at supply and demand...

Mark Keezer
Epileptologist, Centre Hospitalier de l’Université de Montréal
Investigative researcher (chercheur investigateur), Centre de Recherche du CHUM
Assistant clinical professor, Department of neuroscience, Université de Montréal
Epilepsy surgery and remission

Two randomised control trials

80 people with mTLE randomised

Surgery – 58% seizure-free at 1 yr
Medical treatment – 8% seizure-free

Intractable mTLE < 2 yrs after adequate treatment

Had to be terminated due to low recruitment (N = 38)

Surgical group – 11/15 seizure-free at 2yrs
Medical group – 23/23 had seizures.
Cochrane review

RCT and observational studies

177 studies including 16,253 participants

Resective epilepsy surgery (vast majority for temporal lobe epilepsy)

- **8-fold increased chance** of freedom from seizures affecting awareness at 1 year
- **15-fold increased chance** of being seizure-free at 1 year

*Temporal lobe epilepsy*

- 17% relative increase in chance of good outcome

*Non-lesional MRI*

- 20% relative decrease in chance of good outcome.

West, Cochrane 2015
Non-lesional extra-temporal lobe (frontal, occipital, parietal) epilepsy

A SR and MA of observational studies

45% chance of seizure freedom at 1 year in adults
34% chance of seizure freedom at 1 year in children

Long-term outcome

Prospective cohort study of 615 adults (mostly TLE)

52% remained free of disabling seizures at 5 years
47% remained free of disabling seizures at 10 years.

Ansari, Acta Neurochir 2010
deTisi, Lancet 2011
Benefits beyond seizure freedom

Simulation models have shown that epilepsy surgery increases life expectancy by a mean of 5 years

Additional benefits on:

- Cognitive function
- Social outcomes (self-reported improvements in relationships, independence, overall lifestyle)
- Psychiatric comorbidities.

Choi, JAMA 2008
Sherman, Epilepsia 2011
Hamiwka, Epilepsia 2011
Macrodimitrakis, Epilepsia 2011
Risk of epilepsy surgery

**Medical** complications in **2-5% of individuals**
- Infection and haemorrhage, CSF leaks, deep vein thrombosis/pulmonary embolus, pneumonia

**Neurological** complications in **5-11% of individuals**
- Quadrantanopsia (13%) vs hemianopsia (2%)
- Mild or temporary aphasia

**Neuropsychological and psychiatric complications**
- Verbal memory deficits
  - 44% or those with left temporal lobectomy
  - 20 of those with right temporal lobectomy
- Visuospatial memory deficits
  - 20% of individuals, irrespective of side of surgery.

Hader, Epilepsia 2013
Sherman, Epilepsia 2011
Cost-effectiveness

7835 Medicaid uses, aged 18 to 64 years, with drug resistant epilepsy
135 underwent epilepsy surgery between 2000-2008

*Over a mean 5 year period*

Those who underwent surgery had **$7000 per year less costs**

*Considering direct medical costs, excluding pharmaceutical costs and cost of investigations/surgery.*
The underutilization of epilepsy surgery

“...arguably the most underutilized of all accepted therapeutic interventions in the entire field of medicine.”

“...surgical activity must more than triple again just to accommodate the annual increment, let alone to address the backlog...”

Comments based on weak data

1500 surgeries performed = 1992 voluntary survey of 67 US epilepsy centres
5000 surgeries required = 1990 US National Institutes of Health estimate.
More recent data – some uncertainty

UK national survey of all paediatric and adult epilepsy surgeries

- 422 curative treatments (578 total treatments) performed in 2000
- An estimated 450 were required
  
  *Assumed that 50% of presurgical assessments resulted in surgery*

Retrospective administrative data study from Ontario

- 1.2% of individuals with *drug-resistant epilepsy* had surgery (during the following 2-year period)
  
  *Others have reported that 1.5-3% of those *with epilepsy* require surgery*

Lhatoo, Epilepsia 2003
Burneo, Neurology 2016
Uijl, Epilepsia 2008
Indirect evidence of underutilization

Swedish study of a closed population (2001-2002)
  Of 48 individuals with severe focal epilepsy, **28 were not referred** to an epilepsy centre

Dutch study of 10 hospitals
  Of **185 potential candidates**, **116 were not referred** to an epilepsy centre

9 year mean delay before epilepsy becomes drug-resistant
  **20 year mean delay** before referral for a surgical assessment

  *Unchanged over time.*

---

de Flon, Eur J Neurol 2010
Uijl, Epilepsy Res 2012
Berg, Neurology 2003
Indirect evidence - temporal trends

The National Inpatient Sample
20% random sample of non-government USA hospitals

Stable number of surgeries between 1998 and 2009
Despite doubling of the number of admission for focal epilepsy.
A decreasing number of surgeries?

Follow-up to the UK survey from Lhatoo 2003
Survey of all adult and paediatric surgeries
354 curative treatments (710 total treatments) performed in 2010-2011
A 16% absolute decrease from the 422 in 2000-2001

Swedish National Epilepsy Surgery Registry
78 surgeries in 1991
50 surgeries in 2007.

Neligan, Epilepsia 2013
Kumlien, Seizure 2010
How many people require surgery?

Drug resistant epilepsy:

“failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom” (i.e. 12 mos vs rule of 3)
The prevalence of drug resistance

Patients from the Western Infirmary, Glasgow

Only 45% of individuals stopped 1st AED due to inefficacy.

### TABLE 2. SUCCESS OF ANTIEPILEPTIC-DRUG REGIMENS IN 470 PATIENTS WITH PREVIOUSLY UNTREATED EPILEPSY.

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>No. (%)</th>
</tr>
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<tbody>
<tr>
<td>Response to first drug</td>
<td>222 (47)</td>
</tr>
<tr>
<td>Seizure-free during continued therapy with first drug</td>
<td>207 (44)</td>
</tr>
<tr>
<td>Remained seizure-free after discontinuation of first drug</td>
<td>15 (3)</td>
</tr>
<tr>
<td>Response to second drug</td>
<td>61 (13)</td>
</tr>
<tr>
<td>Seizure-free during monotherapy with second drug</td>
<td>41 (9)</td>
</tr>
<tr>
<td>Remained seizure-free after discontinuation of second drug</td>
<td>20 (4)</td>
</tr>
<tr>
<td>Response to third drug or multiple drugs</td>
<td>18 (4)</td>
</tr>
<tr>
<td>Seizure-free during monotherapy with third drug</td>
<td>6 (1)</td>
</tr>
<tr>
<td>Seizure-free during therapy with two drugs</td>
<td>12 (3)</td>
</tr>
<tr>
<td>Total</td>
<td>301 (64)</td>
</tr>
</tbody>
</table>

Kwan, NEJM 2000
Drug resistant epilepsy

A single community in Northern Italy (via GP practices)

Used ILAE definition of DRE

747 individuals with prevalent, 342 with incident epilepsy (2008).

Table 3
Demographic and clinical characteristics of nondrug-resistant and drug-resistant epilepsies in the prevalent and incident populations (n = 684).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category</th>
<th>Prevalent population</th>
<th>Drug-resistant</th>
<th>Incident population</th>
<th>Drug-resistant</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N</td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td></td>
<td>344</td>
<td>302</td>
<td>88.0</td>
<td>39</td>
</tr>
<tr>
<td>F</td>
<td></td>
<td>302</td>
<td>302</td>
<td>100.0</td>
<td>77</td>
</tr>
<tr>
<td>Unclassifiable</td>
<td></td>
<td></td>
<td>76.0</td>
<td>6</td>
<td>24.0</td>
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<tr>
<td>Seizures</td>
<td>Focal</td>
<td>432</td>
<td>365</td>
<td>84.5</td>
<td>67</td>
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<tr>
<td>Generalized</td>
<td></td>
<td>227</td>
<td>195</td>
<td>86.0</td>
<td>34</td>
</tr>
<tr>
<td>Syndromes</td>
<td>PI</td>
<td>44</td>
<td>43</td>
<td>97.7</td>
<td>1**</td>
</tr>
<tr>
<td>PS</td>
<td>253</td>
<td>209</td>
<td>82.6</td>
<td>44</td>
<td>17.4</td>
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<tr>
<td>PC</td>
<td>157</td>
<td>134</td>
<td>85.4</td>
<td>23</td>
<td>14.6</td>
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<tr>
<td>GI</td>
<td>129</td>
<td>117</td>
<td>90.7</td>
<td>12</td>
<td>9.3</td>
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<tr>
<td>GC/GS</td>
<td></td>
<td>74</td>
<td>51</td>
<td>71.8</td>
<td>20</td>
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<tr>
<td>Undetermined</td>
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<td>24</td>
<td>19</td>
<td>79.2</td>
<td>5</td>
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<tr>
<td>Special</td>
<td></td>
<td>6</td>
<td>4</td>
<td>66.7</td>
<td>2</td>
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<tr>
<td>Age**</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>k15 y</td>
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<td>100</td>
<td>76</td>
<td>76.0</td>
<td>24**</td>
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<tr>
<td>15–34 y</td>
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<td>162</td>
<td>139</td>
<td>85.8</td>
<td>23</td>
</tr>
<tr>
<td>35–44 y</td>
<td></td>
<td>207</td>
<td>170</td>
<td>82.1</td>
<td>37</td>
</tr>
<tr>
<td>55–24 y</td>
<td></td>
<td>148</td>
<td>127</td>
<td>85.8</td>
<td>21</td>
</tr>
<tr>
<td>75+ y</td>
<td></td>
<td>67</td>
<td>65</td>
<td>97.0</td>
<td>2</td>
</tr>
<tr>
<td>Disease duration at the time of diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>k1 y</td>
<td></td>
<td>609</td>
<td>512</td>
<td>84.1</td>
<td>97</td>
</tr>
<tr>
<td>y x1 y</td>
<td></td>
<td>72</td>
<td>62</td>
<td>86.1</td>
<td>10</td>
</tr>
<tr>
<td>Missing data</td>
<td></td>
<td></td>
<td>3</td>
<td>100.0</td>
<td>0</td>
</tr>
</tbody>
</table>

W = women; M = men; PI = partial idiopathic; PS = partial symptomatic; PC = partial cryptogenic; GI = generalized idiopathic; GC/GS = generalized cryptogenic/generalized symptomatic; y = years.  
P = 0.0025; **P = 0.0019; ***P = 0.0054 (compared with nondrug-resistant epilepsy). * In the incident population, age was calculated at diagnosis.
A systematic review of DRE

Preliminary Findings of a Systematic Review and Meta-Analysis of The Burden and Predictors of Drug Resistant Epilepsy

Bushra Sultana, Jacynte Comtois, Marie-Andrée Panzini, Ariane Veilleux-Carpentier, Prisca Bauer, Churl-Su Kwon, Genevieve Gore, Colin Josephson, Nathalie Jetté, Mark Keezer

Introduction and Objectives
A proportion of people with epilepsy continue to have recurrent seizures despite optimal pharmacological treatment. The burden of drug resistance and its predictors remains uncertain. Different studies have reported widely varying estimates, using varying definitions of drug resistance. We aim to conduct a systematic review and meta-analysis to identify the incidence and prevalence of drug resistant epilepsy as well as the predictors and correlates for this condition.

Methods
For this study, we developed a search strategy in consultation with a medical librarian. The full study protocol is published in the PROSPERO international prospective register of systematic reviews. 84 articles were identified for inclusion and each was independently reviewed for data extraction and risk of bias assessment by two authors.

Results

Conclusion
Our preliminary results demonstrate a wide range of incidence and prevalence estimates for drug resistant epilepsy (DRE). A more complete and accurate understanding of the burden of DRE and its predictors will allow for better patient counselling and a more accurate understanding of the number of potential candidates for epilepsy surgery.
Relapsing-remitting epilepsy

Western Infirmary, Glasgow

60% of individuals became seizure-free for at least 1 year (over a median period of 5 years) with their 1\textsuperscript{st} or 2\textsuperscript{nd} AED

20\% of the remainder entered terminal remission for at least 1 year over a 7-year period
A further 30\% had ≥50\% seizure reduction

Even amongst those with drug resistant epilepsy

5\% enter 6-month terminal remission each year.

Kwan, NEJM 2000
Neligan, JNNP 2012
Callagnan, Ann Neurol 2007
Relapsing-remitting epilepsy

256 patients with ≥ 1 year seizure-freedom

5 years after onset of remission:

60% remained in remission
10% had relapsed (due to reversible cause) → regained remission
30% relapsed without known reversible cause

Of those who relapsed

53% developed drug resistant epilepsy
40% re-entered remission
7% other (e.g. short follow-up).

Schiller, Arch Neurol 2009
Reasons for the stagnant (or decreasing!) number of surgeries

**Inaccurate results** from administrative database-based studies?

- How does one use ICD codes to identify individuals with DRE?
- How does one use ICD codes to identify individuals who underwent epilepsy surgery?
Reasons for the stagnant (or decreasing!) number of surgeries

Shift in surgery from high volume to lower volume centres.

Englot, J Neurosurg, 2013
Depletion of eligible candidates?

Improved management of *febrile status epilepticus* in children?
And the subsequent decrease in the incidence of mesial temporal lobe epilepsy

*Increasingly frequent surgery among children?* (to explain any decrease in adults)
Represent an increasing proportion of total surgeries done

1110 of 3621 procedures in one USA study (2012)
112 of 354 curative treatments in one UK study (2010-2011).

Helmstaedter, Eur J Neurol 2014
Kaiboriboon, Epilepsy Res 2015
Carlson, Epilepsy Curr 2013
Neligan, Epilepsia 2013
Depletion of eligible candidates?

Are we increasingly focused on more complex candidates?
- Decreasing number of “standard” temporal lobectomies
- Some report increasing delays for epilepsy surgery

Increasing success of newer medical treatments?
- Modest increased efficacy of some 3rd generation AEDs (e.g. LEV)
- Increasing number of AEDs available.

Helmstaedter, Eur J Neurol 2014
Kaiboriboon, Epilepsy Res 2015
Carlson, Epilepsy Curr 2013
Neligan, Epilepsia 2013
Conclusions

We are not doing enough for our patients with DRE
   I am convinced largely due to indirect evidence

We have some data on the number of surgeries performed (i.e. the SUPPLY)
   We have a very difficult time understanding the DEMAND

The number of surgeries performed is stagnant or decreasing
   Depletion of available pools BUT continuing untapped/isolated pools.
Future directions

**Prospective cohort studies**, with multiple methods of case ascertainment, carefully designed to study:
- Those eligible for/require surgery
- Those that are referred to an epilepsy surgery centre
- Those that undergo surgery

Public health policy: strategies to **reduce barriers, increase facilitators**
- To get at that untapped pool.
Thank you.
Questions/comments for the end.